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EXAMINER

SAUNDERS, DAVID A

ART UNIT

PAPER NUMBER

1644

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3/

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

Applicant(s)

Examiner

Group Art Unit

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3/7/03

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1-22, 25-34 is/are pending in the application.
- Of the above claim(s) 14-22 is/are withdrawn from consideration.
- Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-13, 25-34 is/are rejected.
- Claim(s) _____ is/are objected to.
- Claim(s) _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☒ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other _____

Office Action Summary

Art Unit: 1644

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/7/03 has been entered.

The amendment filed on 3/7/03 (Paper 29) has been entered. Claims 1-22 and 25-34 are pending. Claims 1-13 and 25-34 are under examination.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 5 is not enabled, since it is not clear that the Mab' L6 is publically available.

Applicant's response does not overcome, since the exhibit of instructions to authors is from a 1997 issue of PNAS, which applicant takes as the filing date. Since applicant is claiming an effective U.S. filing date of 9/30/93. A showing of journal policies in 1997 is not sufficient.

The examiner fails to understand why prosecution of this issue has been excessively protracted. The PNAS article showing the L6 Mab is by Hellstrom et al. Hellstrom et al. have U.S. patents reciting L6. If the L6 in the Hellstrom patents is the same as that intended by applicant, applicant is required to state so on the record. This would overcome (Paper 20, page 3).

Art Unit: 1644

Claims 1-13 and 25-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 34 recite new matter.

In part C) of each the language regarding "two partially overlapping PCR primers during a PCR reaction that links the first variable domain and the second variable domain" is new matter. Applicant's summary, abstract, and original claims did not disclose this concept as an essential element of the invention. While such oligonucleotide primers "linker-anti" and "linker sense" are incidently mentioned in Example 2, it is to be noted that this recitation in Example 2 is in reference to two specific "linker-anti" and "linker-sense" constructs disclosed in Example 1 and in Tables 2 and 3. Beyond reciting the linkers specifically encoded by these oligonucleotide, applicant has no descriptive support for reciting the method of step C) in a generic sense.

Claims 1-13 and 25-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 34 are indefinite by virtue of reciting part C) as a separate, invented element of the invention. Applicant is claiming a polypeptide compound. A method step in its synthesis is not a distinct element of the compound per se. While applicant's response has indicated that part C) is intended to explain how the elements of A) and B) are constructed, the claim format remains improper. Applicant may overcome by deleting part C) and inserting the material

Art Unit: 1644

therein as a "whereby/wherein" clause, at the conclusion of part B). If the present claim format is not an issue under 112, at the very least, it is an issue under 37 CFR 1.75 (I) with respect to the listing of the elements of the claimed invention.

Regarding the prior art rejection of record, applicant has continued to argue the issues pertaining forming the linkers between the V-H and the V-L segments of the SCFv portion (s) of the claimed polypeptide. The examiner will herein below state new grounds of rejection employing ^{e r a l}Houston (5,258,498) in lieu of ^{e r a l}Huston (5,132,405). The rational for rejection is the same as that set forth in previous actions. The '498 reference is a CIP of the parent of the "405 reference; the former discloses more concerning linkers. The '498 reference is citable under 102(e) and its corresponding publication WO 88/09344 is citable under 102(b).

Claims 1-9, 25-27, 30 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al (Brit. J. Cancer, 65,235,1992), or Seeman et al. (EP 0,050,215/CA 2,062,047) or Eaton et al. (EP 0,392,745) in view of Huston et al. (5,258,498 or WO 88/09344) and Bosslet et al. (5,591,828 or EP 0,040,097).

Eaton et al. disclose a fusion protein comprising an Fab (anti-NP) and an E. Coli. beta=lactamase (Example 15).

The Bosslet et al. And Seeman et al. Primary references have essentially the same disclosure showing a fusion protein comprising a Fab (derived from a humanized version of anti-CEA antibody 431), a linker, and a human B-glucuronidase.

Art Unit: 1644

The fusion proteins of Eaton et al., Bosslet et al. and Seeman et al. differ from that instantly claimed by virtue of having an Fab (composed of H and L chains) instead of having an antigen binding region compound of a single polypeptide (i.e. a BABS or "sFv") formed from VH and VL segments. Huston et al. teach that such an antigen binding region may be present in one or in multiple copies (e.g. col. 7; lines 3-13; col. 12, lines 18-28). They teach that antigen binding regions are formed of VH and a VL binding domains which are joined by a peptide spacer ("linker"); the preferred linker is (GlyGlyGlyGlySer) 3 which is precisely the same linker as that employed by applicant (instant Table 1, see underlined residues at positions 121-135). See Huston et al. at (col. 3, lines 49-52; col. 22, lines 38-59). The one or more antigen binding regions may be linked/fused to other functional regions, such as enzymes (e.g. col. 6, lines 65-68; col. 10, lines 40-44; col. 13, lines 11-15).

For clarification, it is noted that Huston et al. designate the polypeptide segment linking the VH and VL segments as a "spacer" and the polypeptide segment linking the binding site (s) to the enzyme as a "linker". Applicant's designation for both of these is a linker.

The essence of the obviousness rejection is that it would have been obvious to modify the fusion protein constructs of the primary references by substituting the single chain antigen binding polypeptides of Huston et al. for the Fab of the construct of Eaton et al., Bosslet et al. or Seeman et al. Motivations to make this substitution are as follows:

Art Unit: 1644

1) Huston et al. teach enzymes can be fused to the antigen binding region(s). One would have hence fully expected the glucuronidase enzyme taught by Bosslet et al. or Seeman et al. to be useable when fused to the single chain constructs of Huston et al.

2) One of ordinary skill in the art would have recognized Fab, Fv and the single chain constructs of Huston et al. as Functional equivalents in terms of antigen binding. See Huston et al. at col. 8, lines 5-8; col. 9, lines 27-68.

3) One would have been motivated to use the sFv/BABS constructs of Huston et al. in lieu of Fab since the former have increased stability, less immunogenicity, better penetration of body tissue, enhanced clearance, and more economical production methods in comparison to whole antibodies or their fragments. See col. 8, line 54 - col. 9, line 6; col. 12, line 60 - col. 13, line 15.

4) One would have expect an inherent advantage to be gained by using the single chain constructs of Huston et al. in that one would only need to transfect cells with one instead of two vectors in order to obtain expression of the protein. Compare Huston et al. at col. 23, lines 47-57 with Bosslet et al. at page 235, col. 1, last paragraph.

From the above considerations, the polypeptide product of instant claim 34, which requires only one sFv region would have been obvious; with respect to the polypeptide product of claim 1, which requires at least two sFv regions note the following.

5) One would have been motivated to provide the constructs of Huston et al. with two or more antigen binding regions because such would increase the overall affinity/avidity of

Art Unit: 1644

the protein when binding to cell surfaces that present multiple copies of the antigen. See Huston et al. at col. 7, lines 3-10. See Bosslet et al. ('097) at Fig. 3 and discussion associated therewith for a teaching of how a polypeptide can be provided with two oppositely oriented antigen binding regions within a single polypeptide.

6) From the above considerations set forth in parts 3) and 5) one would have expected that, due to the lower size of sFv compared to Fab, one would have been able to provide a construct that has at least bivalency for antigen (as opposed to monovalency when one provided an Fab) without significantly increasing the size of the construct over that containing a Fab. One would have thus gained the above noted advantage of increased affinity/avidity without significant loss of tissue penetrating capacity of the polypeptide.

As to limitations set forth in dependent claims that have not been explicitly or implicitly addressed supra, note the following.

When the fusion protein is expressed in a eukaryotic host (Huston et al. at col. 15, lines 32-36; col. 20, lines 5-7 and 20-35, one would have expected the polypeptide to be inherently glycosylated in accord with instant claims 2 and 9.

Claims 25 and 33 are directed to a pharmaceutical composition and method of treatment. The Bosslet et al. disclosure teaches potential therapeutic use (page 238). Seeman et al. likewise teach use of the fusion proteins in humans (page 1). The above noted portions of Huston et al. teaching improved tissue penetration clearly have a body treatment in consideration. Thus claims 25 and 33 would have been obvious.

Art Unit: 1644

Claim 26 is drawn to a diagnostic composition or use thereof. This claim recites merely an intended use that carries no weight and does not distinguish the polypeptide from what it would be in any composition in which it would bind to antigen and have enzymatic activity. Clearly such compositions would include those wherein the antigen binding and enzymatic activity of the polypeptide is evaluated --e.g. Bosslet et al. at pages 235-236, Huston et al. at col. 21, lines 55+.

Claims 27 and 30 require that the prodrug activating enzyme be a beta-lactamase, which is taught by Eaton et al. as a prodrug-activating enzyme. They further point one to use of this enzyme obtained from *B. Cereus* (page 4, line 14.

Claims 1, 11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al., or Seeman et al. or Eaton et al. in view of Huston et al. and Bosslet et al. as applied to claims 1-9, 25-27, 30 and 33 above, and further in view of Ong et al. (Cancer Res. 51. 619, 1991 and Bagshawe et al. (WO 89/10140).

Huston et al. (col. 15, lines 27+; col. 20, lines 8+; col. 21, lines 34-54) teach that polypeptides containing sFv may be produced in Gram-negative bacteria, such as *E. Coli.*, and be properly refolded with the correct conformation. Since *E. Coli* are more easily grown than many eukaryotic cells (col. 9, lines 2-6), such as myeloma cells, one would have been motivated to use an *E. Coli* expression system capable of providing correctly folded proteins in large amounts. One of ordinary skill would have recognized that polypeptides produced by *E. Coli* would not be glycosylated.

Art Unit: 1644

Ong et al. teach that it is advantageous to permit rapid clearing of circulating therapeutic antibodies in a treated individual by providing galactosyl moieties on the antibodies. These authors particularly teach that such clearing would be advantageous in cases wherein antibody-enzyme conjugates that convert a prodrug to an active drug are employed. Since, as noted supra in the rejection of claim 1, antibody-enzyme conjugates and sFv-enzyme fusion proteins are functionally equivalent, it would have been obvious to provide galactosyl moieties on sFv-enzyme fusion proteins, so that these could be rapidly cleared from the circulation. One of ordinary skill would have known that when a polypeptide is expressed in a prokaryote, such as *E. Coli*, as taught by Huston et al.; there is no glycosylation, and hence, such an expressed polypeptide would be subsequently glycosylated with galactose moieties according to a chemical method, such as that taught by Ong et al. (page 1620), col. 1).

Bagshawe et al. will also be relied upon for teaching the desirability of placing galactosyl and/or mannosyl moieties on an antibody that is a member of an antibody-prodrug activating enzyme conjugate. See page 10, lines 6-25. The blocking and clearing strategy taught therein is akin to that taught by Ong et al. at pages 1622-1624. From the teachings on Ong et al. and Bagshawe et al., either together or each alone, one would have ample motivation to provide galactosyl or other carbohydrates residues taught by Bagshawe et al. (page 13) on sFv-enzyme fusion proteins.

It is further noted that, even if one choose to produce the sFv fragments in mammalian cells, such as the hybridoma cells taught by Huston et al., one would still have motivation to

Art Unit: 1644

provide galactosyl/mannosyl residues on the antibodies beyond the degree of glycosylation obtained upon host cell expression. Note that Bagshawe et al. (WO 89/10140) and Ong et al. provided galactosyl moieties on monoclonal antibodies which were already galactosylated.

Claims 1, 10, 13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al., Seeman et al. or Eaton et al. in view of Huston et al. and Bosslet et al. and further in view of Ong et al. and Bayshawe et al. as applied to claims 1, 11-12 and 32-33 above, and further in view of Goochee et al. (Biotechnol., 9,1347,1991).

The above rejections have noted that one would have realized that it would have been desirable to provide a galactosylated or mannosylated polypeptide in order to enhance clearance of unbound polypeptide from the circulation.

Goochee et al. at page 7 show that it was known that yeast could be used to express polypeptide having a high degree of manosylation and having a rapid clearance rate. It hence would have been obvious to express the polypeptide of claim 1 in such yeast in order to provide polypeptide having mannose moieties that would allow for effective clearance of the polypeptide.

The species recited in claim 13 is specifically taught by Goochee et al. at page 1348. The species recited in claim 29 is not specifically taught at page 1348; however, Goochee et al. teach most yeast strains provide such mannose moieties and it would have been within the ordinary skill of one in the art to determine which yeast species and strains would be appropriate.

Art Unit: 1644

Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over ;Bosslet et al. Seeman et al. or Eaton et al. in view of Huston et al. and Bosslet et al. as applied to claims 1-9, 25-27, 30 and 33 above, and further in view of Bagshawe et al. (WO 88/07378).

Bagshawe et al. show the further feature that it was known and conventional to provide carboxypeptidase G2 from pseudomonas as a prodrug activating enzyme in antibody enzyme conjugates for therapy.

In view of the above newly stated grounds of rejection that rely upon Huston et al. ('498) in lieu of Huston et al. ('405), the examiner is not under obligation to respond to applicant's arguments set forth in Paper 29. However, since the instant rejections parallel those of record the examiner will argue salient points as follows:

1) Applicant's arguments earlier in prosecution (e.g. filed 11/7/00 and 1/5/01) have focused on the unpredictability of choosing an appropriate linker sequence between the VH and VL segments. This is a baseless argument, since the one and only polypeptide linker specifically taught by applicant is (GlyGlyGlyGlySer)₃, which is precisely the linker taught by Huston et al. as preferred. See col. 22, lines 39-59.

2) Applicant's arguments, in the responses of 7/12/02 and 3/7/03 concerning the manner in which the linker is constructed, in accord with part C) of claims 1 and 34, are without merit. Whether or not Huston et al. used the same method as applicant to construct the linker, both Huston et al. and applicant end up with the same linker (GlyGlyGlyGlySer)₃ in the polypeptide product. Applicant's arguments have not shown that the claimed product, when

Art Unit: 1644

produced in accord with the limitations of part C) of claims 1 and 34, results in a materially different polypeptide product, in terms of the amino acid sequence of the linker. Given this fact, applicant's verbose arguments with respect to the linker^{re} require no further response from the examiner.

3) Applicant's contention that Huston et al. do not teach fusion polypeptide are obfuscatory, in view of the clear, art understood meaning of the term "fusion" polypeptide. In any event, it is clear that Huston et al. teach polypeptide encoded by a single DNA, as applicant deems to be a proper definition of "fusion" protein instantly. See Huston et al. at, for example, col. 2, lines 50-64; col. 9, lines 7-21; col. 13, lines 18-36; col. 14, line 9 - col. 15, line 26.

4) The examiner concurs that Eaton et al. teach Fv, not sFv. The above newly stated rejection has employed the teachings of Eaton et al. in Example 15 of an Fab enzyme fusion construct, similar to that of Bosslet et al. (Brit. J. Cancer) or Seeman et al.

5) Applicant has argued that there is no motivation to use E. Coli as a host in lieu of a Mammalian cell as a host. Applicant urges that the examiner has cited no authority. The examiner does not consider this necessary, since any one of minimal skill knows that mammalian cells are more fragile and require more coplox media (e.g. with serum or growth factors) than bacteria. Nevertheless, it is noted that Huston et al. teach production in bacteria is more economical (col 9, lines 2-6), which fact reflects the above consideration; the argument is moot, anyway since the newly stated rejection has noted that Ong et al. and Bagshawe et al.^{teach} that galactosylation of hybridoma produced Mabs is desirable for enhancing clearance.

Art Unit: 1644

6) Applicant's arguments concerning the tertiary references of Ong et al., Bagshawe et al. and Goochee et al. argue these references in isolation from the primary and secondary references. Huston et al. clearly teach that sFv antibodies are useful and desirable alternatives to the whole antibodies or fragments thereof taught by the tertiary references. The latter are relied upon for teaching the desirability of placing galactosyl/manosyl moieties on antibodies having any kind of construct and for teaching how to chemically or biologically provide such moieties upon the antibodies.

Herein below rejections based upon Winter et al. have been modified.

Claims 1-4, 8-9, 25-26 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. (6,248,516) in view of Huston et al. (5,258,498 or WO88/09344).

Winter et al. teach constructs containing single domain ligands and therapeutic compositions and uses thereof. The single domain ligands include sFvs (col. 11, lines 38-61, espec. lines 55-58; also col. 13, lines 52-55).

The single domain ligands of Winter et al. can be linked to an effector molecule, such as an enzyme which activates a prodrug (col. 4, lines 53-56), and such linkage may be achieved by forming a fusion product, with or without a linker peptide (col. 5, lines 45-52 and col. 12, lines 4-12).

Winter et al. further teach that the constructs may contain multiple single domain ligands, which can be linked to an effector molecule (col. 5, lines 42-44), which as discussed above can be a prodrug activating enzyme. Winter et al., teach that providing constructs with multiple

Art Unit: 1644

compels of the same ligand provides for larger molecule which is less readily filtered from the circulation by the kidneys (col. 5, lines 36-38). The constructs can also be provided with two single domain ligands against different epitopes of an antigen, or against different antigens, in order to enhancing binding to cell surfaces (col. 5, lines 24-35). Applicant's claim 1 encompasses either the case in which both antigen binding regions have the same binding specificity or the case in which each has a different binding specificity.

Winter et al.'s teachings regarding the sFv ligands are not clear as to whether or not there may be linkers between the VH and VL segments of the sFv. The teachings of Huston et al. have been reviewed further supra. As noted therein, Huston et al. teach the provision of the linker (GlyGlyGlyGlySer)₃ between the VH and VL segments. No weight is given as to how these are made in applicant's step C) of claims 1 and 34.

Regarding dependent claim features not discussed supra, note that for claims 2 and 9 Winter et al. teach expression of the constructs in mouse myeloma cells (e.g. col. 19, lines 59-62)' these would inherently glycosylate any expressed fusion protein.

With respect to claim 4, note Winter et al. teach the constructs can be used to treat tumors (col. 4, lines 43, 62; col. 5, line 33).

Claims 1-2, 4-5, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. In view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Seeman et al. (EP 0,501,215 or CA 2,062,047).

Art Unit: 1644

Winter et al. have been discussed supra for teaching constructs containing one or multiple sFv regions, that bind to tumor cells, fused to a pro-drug activating enzyme. Winter et al. do not teach specific tumor antigens or specific prodrug activating enzymes.

Seeman et al. teach therapeutic fusion proteins with binding specificity for CEA and with human B-glucuronidase activity. Since CEA is a known tumor antigen and since human B-glucuronidase is a known prodrug activating enzyme, provision of these particular features in the single domain ligand structures of Winter et al. would have been obvious.

Regarding claims 2 and 9, expression in BHK cells, as taught by Seeman et al. (page 10). would inherently yield glycosylated fusion proteins.

Claims 1, 6, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. In view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Eaton et al.

Winter et al.'s teachings have been discussed supra. They do not teach B-lactamase as a prodrug activating enzyme. Eaton et al. teach tht such enzymes were art known in antibody enzyme conjugates. They teach the B-lac^tamase from B. Cercus (page 4, line 14). Thus it would have been obvious to provide this enzyme in the single domain ligand compositions of Winter et al.

Claims 1, 6 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Bagshawe et al. (WO 88/07378).

Art Unit: 1644

Winter et al.'s teachings have been reviewed supra. They do not teach carboxypeptidase G2 from pseudomonas as a prodrug activating enzyme. Bagshawe et al. show that this was a known prodrug activating enzyme in antibody enzyme conjugates. It hence would have been obvious to provide this ^{fused to} enzyme the single domain ligand ^{binding} composition of Winter et al.

Claims 1-2, 9, 11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Huston et al. as applied to claims 1-4, 8-9, 25-26 and 33-34 above, and further in view of Ong et al. and Bagshawe et al. (WO 89/10140).

Winter et al. teach that their constructs may be produced in bacteria (col. 11, lines 8-11). Also, as noted supra Huston et al. teach production in bacteria; one would have recognized that any fusion protein construct produced by bacteria would not be glycosylated.

Ong et al. teach that it is advantageous to permit rapid clearing of circulating therapeutic antibodies in a treated individual by providing galactosyl moieties on the antibodies. These authors particularly teach that such clearing would be advantageous in cases wherein antibody-enzyme conjugates that convert a drug to active drug are employed. Since, antibody-enzyme conjugated and sFv-enzyme fusion proteins are functionally equivalent it would have been obvious to provide galactosyl moieties on sFv-enzyme fusion proteins so that these could be rapidly cleared from the circulation. One of ordinary skill would have known that when a polypeptide is expressed in a prokaryote, such as E. Coli (taught by Winter et al. or Huston et al.) there is no glycosylation, and hence, such an expressed polypeptide could be subsequently

Art Unit: 1644

glycosylated with galactose moieties according to a chemical method, such as that taught by Ong et al. (page 1620), col. 1).

Bagshawe et al. will also be relied upon for teaching the desirability of placing galactosyl and/or mannosyl moieties on an antibody that is a member of an antibody-prodrug activating enzyme conjugate. See page 9, lines 1-5 and page 10, lines 6-25. The blocking and clearing strategy taught therein is akin to that taught by Ong et al. at pages 1622-1624. From the teachings of Ong et al. and Bagshawe et al., either together or each alone, one would have ample motivation to provide galactosyl or other carbohydrates residues taught Bagshawe et al. (page 13) on the sFv-enzyme fusion proteins, of Winter et al.

Claims 1, 10 13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Huston et al. and further in view of Ong et al. and Bayshawe et al. as applied to claims 1-2, 9, 11-12 and 31-32 above, and further in view of Goochee et al.

The above rejections have noted that one would have realized that it would have been desirable to provide a galactosylated or mannosylated polypeptide in order to enhance clearance of unbound peptide from the circulation.

Goochee et al. at page 7 show that it was known that yeast could be used to express polypeptide having a high degree of manosylation and having a rapid clearance rate. It hence would have been obvious to express the polypeptide of claim 1 in such yeast in order to provide polypeptide having mannose moieties that would allow for effective clearance of the polypeptide.

Art Unit: 1644

The species recited in claims 10 and 13 are specifically taught by Goochee et al. at page 1348. The species recited in claim 29 is not specifically taught at page 1348; however, Goochee et al. teach most yeast strains provide such mannose moieties and it would have been within the ordinary skill of one in the art to determine which yeast species and strains would be appropriate.

Applicant's traversal of the prior art rejections of record based upon Winter et al. have focused on the fact that Winter et al. do not teach forming linkers as recited in part c) of claims 1 and 34. Since the rejection now relies upon Huston et al., as a secondary reference teaching the exact linker having the exact amino acid sequence exemplified by applicant, the point is moot. As argued further supra, the method of creating the linker sequence, as recited in part C), is not relevant in considering the polypeptide product, because this method results in a linker no different from that taught by Huston et al.

Applicant's urgings of 3/7/03 have been considered but are unconvincing.

Herein below new grounds of rejection are stated for new claim 34.

Claim 34 is rejected under 35 U.S.C. 102(a) as being anticipated by Bagshawe (WO 93/13805).

Bagshawe teaches constructs of an antibody or binding site thereof and a prodrug activating enzyme. The antibody binding site can be a sFv with the VH and VL domains linked by a flexible oligo peptide. See page 6, line 15; page 7 line 7, particularly page 6, lines 20-21. The antibody binding site and enzyme can be chemically cross-linked or fused. See page 15,

Art Unit: 1644

lines 6-29. All that is required for anticipation of claim 34, part C) is teaching of an oligopeptide linker.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP 201.15,

Claim 34 is rejected under 35 U.S.C. 102 (e) as being anticipated by Hellstrom et al. (5,869,045).

Hellstrom et al. show the instant invention in claim 7, if base claim 1 is read with the embodiment recited in dependent claim 4. Regarding the construction of the sFv, note col. 27, lines 21-30 teach that the ScFv can be constructed with a peptide bridge between the VH and VL domains. Also note col. 75, lines 36-55 teaching that the sFv is formed by PCR and is provided with a synthetic linker (GlyGlyGlyGlySer)₃, which is exactly the same as that exemplified by applicant.

Claim 34 is rejected under 35 U.S.C. 102(e) as being entirely anticipated by Borstel et al. (6,258,360).

Borstel et al. show fusion proteins having a single chain antibody, directed against a target cell (e.g. cancer cell), and a catalytically active polypeptide (either an enzyme or an abzyme) that activates a prodrug. Note giving the broadest reasonable interpretation to "enzyme" in applicant's claim it is considered that this encompasses both the enzyme and abzyme (catalytically active antibody) of Borstel et al. See col. 6, line 27 - col. 9, line 34; col.

Art Unit: 1644

50, line 41 - col. 52, line 18; col. 55, line 1 - col. 56, line 53. Note that these constructs contain a polypeptide linker sequence (col. 9, line 9; col. 56, lines 22-53). This is sufficient to anticipate part C) of claim 34.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D., whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday-Thursday from 8:00 a.m. to 5:30 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christian Chan, can be reached on (703) 308-3976. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

D. Saunders:jmr

April 22, 2003

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644